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**Non-motor symptoms in patients with uncertain Parkinsonism and Scans Without
Evidence of Dopaminergic Deficit (SWEDDs)**

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Abstract

Objectives: To assess the occurrence of non-motor features and symptom progression in patients with uncertain Parkinsonism and Scans Without Evidence of Dopaminergic Deficit (SWEDDs), patients with early Parkinson's disease (PD), and healthy controls.

Methods: Non-motor data for 62 patients with SWEDDs, a cross-matched sample of PD patients (n=62) and a population of healthy controls (n=195) were accessed from the Parkinson's Progressive Marker's Initiative (PPMI). Data included scores from seven validated clinical questionnaires examining a range of non-motor features including sleepiness, geriatric depression, REM sleep behaviour, State-Trait anxiety, autonomic function and olfactory function. All non-motor symptoms were compared among subjects at baseline, one year and two years of follow up.

Results: SWEDDs had more excessive daytime sleepiness than both PD and healthy subjects (p value <0.001) and also had worse cardiovascular and thermoregulatory dysfunction (p value = 0.031 and p value = 0.019) compared to PD. SWEDDs had a significantly better sense of smell than PD patients (p value <0.001) but worse olfaction than healthy controls (p value = 0.005). There was a positive correlation between sleepiness and autonomic dysfunction in SWEDDs patients (Spearman's Rank R=0.502 p<0.001). Follow up analysis of patient groups showed stable non-motor phenotypes with no significant fluctuation in questionnaire scoring over two years.

Conclusion: At an early symptomatic stage, SWEDDs exhibit non-motor features that differ from PD patients involving cardiovascular, olfactory, sleep and thermoregulatory function. Our results suggest that the use of questionnaires to identify non-motor symptoms may help differentiate SWEDDs from PD patients at the time of diagnosis.

Abstract 252 words

Introduction

Imaging dopaminergic function has identified a subset of patients who, despite manifesting symptoms and signs suggestive of Parkinson's disease (PD), have normal dopaminergic function. These patients have been labelled as having Scans Without Evidence of Dopaminergic Deficit (SWEDDs) and represented 4-15% of patients diagnosed with idiopathic early PD across clinical trials.(Fahn, 2005) Evidence suggests that SWEDDs do not have PD pathology: not only does the nigrostriatal function of SWEDDs patients remain normal over 2-5 years follow-up, but most do not deteriorate or respond to Levodopa therapy.(Fahn, 2005)(Mian, Schneider, Schwingenschuh, *et al.*, 2011) A number of studies have identified adult onset dystonic tremor as one cause of SWEDDs with patients being misdiagnosed with PD despite exhibiting clinical features of dystonia.(Schwingenschuh, Bhatia, Schneider, *et al.*, 2010)(Schneider, Edwards, Mir, *et al.*, 2007) Essential tremor, vascular parkinsonism, and drug-induced parkinsonism should also be considered as diagnoses in patients with parkinsonism who are SWEDDs.(Bajaj, 2010)

While the motor symptoms of SWEDDs mimic those occurring in PD patients, little is known regarding the non-motor features of this population. Previous studies have found SWEDDs to have significantly fewer non-motor symptoms(Jang, Ahn & Kim, 2013)(Schwingenschuh, Bhatia, Schneider, *et al.*, 2010) and significantly better olfaction than PD patients.(Silveira-Moriyama, Schwingenschuh, O'Donnell, *et al.*, 2009a) Moreover, while non-motor symptoms worsen over time in PD patients,(Antonini, Barone, Marconi, *et al.*, 2012) no reports on the progression of non-motor symptoms in SWEDDs are available.

The aims of this study were to document the prevalence and progression of non-motor symptoms in SWEDDs in comparison with dopamine deficient PD patients and further augment our knowledge and classification of this population.

Introduction: 228 words

Methods

Subjects and protocol

Our study investigated a random sample of de novo PD patients with abnormally reduced striatal dopamine transporter (DAT) imaging, a cohort of SWEDDS with features of parkinsonism but normal DAT imaging, and healthy controls with normal DAT binding enrolled in the Parkinson's Progression Markers Initiative (PPMI), an ongoing multicentre study, (www.ppmi-info.org/data). Data for baseline assessment was accessed on 14.01.2014 from the PPMI database and data for follow up analysis was downloaded on the 03.07.2014 to allow more time for patients to progress to two years follow up. PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Avid radiopharmaceuticals, Biogen idec, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche and UCB.

The main eligibility criteria for both PD and SWEDDs patients included the presence of at least two of: resting tremor, bradykinesia and rigidity or asymmetric resting tremor and asymmetric bradykinesia according to U.K. Brain Bank criteria for the diagnosis of PD.(Gibb & Lees, 1988) At baseline patients were required to have had a diagnosis for less than two years and be at a Hoehn and Yahr stage of 1-2. Participants were aged over thirty and were not expected to require PD medication within six months from baseline. Patients with and without striatal dopamine transporter binding deficits present on FP-CIT SPECT (DatScan™) were classified as PD or as SWEDDs patients, respectively.

Study variables

We utilised a number of validated clinical questionnaires to assess non-motor symptoms in study participants. Sleep disorders were rated with the Epworth Sleepiness Scale for the severity of excessive daytime sleepiness (EDS) and the REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) for REM Sleep Behaviour Disorder (RBD).REF Depressive symptoms were assessed using the short version of the Geriatric Depression Scale (15-item), which we present alongside the number of patients either diagnosed with depression or taking antidepressants. The State-Trait Anxiety Inventory for adults scored the participants current and general anxiety levels. The Scales for Outcomes in Parkinson's Disease- Autonomic (SCOPA-AUT) Patient Questionnaire measured autonomic dysfunction as a function of six individual domains: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillary and sexual. Symptoms assessed include swallowing difficulties and bowel problems in the gastrointestinal domain, retention, incontinence and frequency in the urinary domain, light-headedness and fainting in the cardiovascular domain, difficulties in tolerating heat and cold in the thermoregulatory domain, sensitivity to light in the pupillary domain and finally maintaining arousal and achieving orgasm in the sexual domains. The MDS-UPDRS 1 scored non-motor symptoms REF and the University of Pennsylvania Smell Identification Test (UPSIT) measured olfactory function in participants.

The presence of excessive daytime sleepiness (EDS) was defined by a score >10 on the Epworth Sleepiness Scale.(Johns, 1991) REM Sleep behaviour disorder was diagnosed using a cut off value of 5 on the RBDSQ.(Stiasny-Kolster, Mayer, Schäfer, *et al.*, 2007) A GDS threshold value of 5 suggested the presence of depressive symptoms.(D'Ath, Katona, Mullan, *et al.*, 1994) For the UPSIT we classified hyposmia as >2 SDs below the healthy controls (HC's) mean and anosmia as below a score of 18 out of 40.(Deeb, Shah, Muhammed, *et al.*, 2010) For the SCOPA-AUT, patients using a catheter were given 3 points for each urinary

question and those who reported a question concerning sexual functions as not applicable, were removed from the analysis of sexual dysfunction. As a result, we also report the mean SCOPA-AUT total with the sexual analysis excluded.

We used data from the Clinical Diagnosis and Management Questionnaire which was used as part of the PPMI protocol to assess the progression of SWEDDs patients. We focused on the study doctors' clinical diagnoses of the SWEDDs patients.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation. Normality of data distribution was interrogated using the Kolmogorov-Smirnov test. Non-normally distributed data was compared across the three subject groups by the use of Kruskal-Wallis test, applying a Bonferroni correction for the multiple comparisons performed. Categorical variables were expressed as proportions and differences compared with a χ^2 test. Correlations between variables were investigated by the use of Spearman's rank correlation coefficient. Follow up analysis was performed for each diagnostic group separately, with the study visit being the independent variable. All data were interrogated with SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). Statistical significance was accepted at $p < 0.05$.

Methods: 700 words

Results

Baseline analysis of non-motor symptoms

Baseline data for 62 SWEDDs patients, a cross-matched group of 62 PD patients and 195 healthy controls were compared. Patients were matched for age, gender, disease duration and

Hoehn and Yahr staging; their baseline characteristics are reported in Table 1. Table 2 details the mean questionnaire totals with Kruskal-Wallis derived p values for non-motor symptoms.

7.2% of healthy controls, 30.6% of SWEDDs and 8.1% of PD patients had excessive daytime sleepiness (EDS). Pearson's Chi-square test revealed there was a significantly higher prevalence of EDS in SWEDDs than PD patients (χ^2 (1,N=124)=10.127, p=0.001) and healthy controls (χ^2 (1,N=257)=23.145, p<0.001). PD patients and healthy controls had the same prevalence of EDS (χ^2 (1,N=257)=0.054, p=0.817). SWEDDs patients had significantly more severe daytime sleepiness than both healthy controls and PD's (p=0.001 and p=0.01).

The prevalence of REM Sleep Behaviour Disorder (RBD) was 20% in HC's, 41.9% in SWEDDs and 41.9% in PD patients. There was a greater frequency of RBD in SWEDDs than HC's (χ^2 (1,N=257)=11.980, p=0.001). SWEDDs had more severe REM Sleep Behaviour Disorder than the healthy controls (p=0.001) but similar to Parkinson's patients (p=1). PD patients also had more severe RBD than HC's (p=.047). In this cohort of patients, 1 HC, 2 SWEDDs and 1 PD patient had a previous diagnosis of RBD. 6.7% of HC's had features of depression compared to 30.6% of SWEDDs patients and 14.5% of PD's patients. There was a significant increase in the frequency of depressive features in SWEDDs and PD patients χ^2 (1,N=124) =4.613, p=0.032. PD patients did not however have greater depressive features than HC's χ^2 (1,N=257) =3.703, p=0.054. SWEDDs had significantly more severe depressive symptoms than healthy controls (p=0.001) but not more so than PD patients (p=1). The PD patients had increased depressive features compared to HC's (p=.001). PPMI data showed a number of patients to have a formal diagnosis of depression (23 HC's, 16 SWEDDs and 12 PD) yet a larger number were taking medication for the treatment of depression (29 HC's, 17 SWEDDs and 16 PD).

The State Trait Anxiety Inventory has two components Y1 (State anxiety) and Y2 (Trait anxiety). SWEDDs patients had more severe state and trait anxiety symptoms than HC's ($p < 0.001$ and $p < 0.001$) but their levels were not different from PD patients ($p = 1$ and $p = 0.9$). PD patients had higher anxiety than HC's on both state and trait features ($p < 0.001$ and $p = 0.008$).

SWEDDs had a higher SCOPA total score (after excluding sexual function) than both HC's and PD patients, but only the interaction with HC's was significant ($p < 0.001$ and $p = 0.336$). PD patients also had worse autonomic dysfunction than healthy controls ($p < 0.001$). The prevalence of autonomic symptoms and the mean totals for the SCOPA-subdomains are shown in Table 3, the p values included represent the inter-group variance in the prevalence of autonomic symptoms as assessed by Pearson's Chi-Square test. Analysis of SCOPA-AUT subdomains revealed that pupillary was the only domain that did not vary significantly across groups ($p = 0.011$). For urinary, thermoregulatory and sexual domains SWEDDs had significantly more dysfunction than healthy controls (all p values < 0.001) but were similar to PD patients ($p = 0.906$, $p = 0.019$ and $p = 0.067$). This differed from the gastrointestinal and cardiovascular domains where SWEDDs patients were more severely affected than healthy controls (both p values < 0.001) and PD patients ($p < 0.001$ and $p = 0.001$). PD patients had worse gastrointestinal, urinary and cardiovascular problems than healthy controls ($p < 0.001$, $p = 0.011$ and $p = 0.001$) but did not differ from healthy controls in thermoregulatory and sexual domains ($p = 0.207$ and $p = 0.839$).

The MDS-UPDRS-1 Patient questionnaire contains seven questions concerning non-motor symptoms. We found that both SWEDDs and PD patients had a higher severity of these symptoms than healthy controls (both p values $< .001$) but did not differ significantly from each other ($p = 0.268$). PD patients also suffered from more severe symptoms than healthy controls ($p < 0.001$).

19.4% of SWEDDs patients had hyposmia in comparison to 72.6% of PD patients, this difference in prevalence was significant, χ^2 (1,N=124) =35.359, $p<0.001$. There was also a significant difference in the frequency of anosmia between the two groups, with 4.8% of SWEDDs patients reporting loss of sense of smell compared to 29% of PD patients, χ^2 (1,N=124) =12.90, $p<0.001$. SWEDDs had worse hyposmia than healthy controls ($p=.005$), but a significantly better sense of smell than Parkinson's disease patients ($p<.001$). PD patients had significantly worse hyposmia than healthy controls ($p<0.001$).

There was a correlation between ESS and SCOPA-AUT scores between ESS total and SCOPA-total (Spearman's Rank $R=0.523$ $p<0.001$) for SWEDDs patients but only a weak correlation for PD patients (Spearman's Rank $R=0.280$ $p=0.028$). ESS totals were most strongly correlated in SWEDDs patients with thermoregulatory ($R=0.532$ $p<0.001$), pupillary ($R=0.401$ $p=0.001$) and urinary domains ($R=0.376$ $p=0.031$).

Follow up analysis of non-motor symptoms

At the time of analysis, 128 healthy controls, 30 SWEDDs patients and 36 of the PD patients analysed at baseline also had data recorded after one year and two years of follow up. Table 4 outlines participants' mean totals for the clinical questionnaires at each time point (UPSIT was not included as it was only recorded in patients at baseline) and p values representing the variation in questionnaire scoring over the course of the study visit. We found no significant variation in scoring for any clinical questionnaire or diagnostic group over this time period.

Clinical Diagnosis and Management Questionnaire

Figure 1 details the assigned diagnoses of the SWEDDs patients after their most recent visit. There were 7 categories and one third were still labelled as IPD. The 'Other' category

contained one case of valproic acid induced parkinsonism, one case of asymmetric bradykinesia, one case of asymmetric postural tremor, one functional disorder, three cases relating to neuropathy, one case of Primary Lateral Sclerosis, one possible dementia, two cases of unspecified parkinsonism and one case of dystonic tremor.

Results: ~ 934

Discussion

Our study showed that SWEDDs patients had more severe levels of sleepiness, depressive symptoms, REM Sleep Behaviour Disorder, both state and trait anxiety, autonomic dysfunction and a worse sense of smell than healthy controls at baseline. They also experienced significantly worse sleepiness, gastrointestinal and cardiovascular dysfunction compared to PD patients, although they had better olfaction.

Previous research into sleep abnormalities in PD (Gjerstad, Alves, Wentzel-Larsen, *et al.*, 2006) (Gjerstad, Aarsland & Larsen, 2002) (Zoccolella, Savarese, Lamberti, *et al.*, 2011) has suggested an EDS prevalence of 5.6-8% at baseline, which is concordant with the prevalence of 8.1% in PD patients. Circadian rhythm has an important function in sleep regulation and may be mediated by the autonomic nervous system (Morris, Aeschbach & Scheer, 2012) and therefore irregularities of autonomic functioning may contribute to sleep disorders. Although overall autonomic function in SWEDDs was not significantly worse than PD patients, the stronger correlation between autonomic function and sleepiness levels in SWEDDs patients

may partially account for their greater levels of excessive daytime sleepiness than PD patients.

Our study reports greater levels of RBD in SWEDDs and PD patients than healthy controls but no difference between PD patients and SWEDDs. There is an absence of research into RBD in SWEDDs patients, but previous studies into the prevalence of RBD in PD have shown RBD to be present in 25-40% of patients.(Chahine, Daley, Horn, *et al.*, 2013a) Two recent studies of over 400 PD patients, one using video supported polysomnography and one using the RBDSQ to diagnose RBD, found the overall frequency of RBD to be 45-47%.(Sixel-Döring, Trautmann, Mollenhauer, *et al.*, 2011)(Rolinski, Szewczyk-Krolikowski, Tomlinson, *et al.*, 2014) In line with these findings, we found that 41.9% of PD patients in this cohort had RBD. The precise pathological mechanisms underlying RBD are still unknown but dopamine dysfunction is not thought to be the sole factor,(Iranzo, Santamaria & Tolosa, 2009) instead abnormal functioning in glutamatergic, GABAergic, serotonergic and noradrenergic pathways are thought to be involved.(Iranzo, Santamaria & Tolosa, 2009)(Lima, 2013). Depression is a symptom often unrecognised in PD(Weintraub, Moberg, Duda, *et al.*, 2003) and contributes to functional disability in daily living.(Ravina, Camicioli, Como, *et al.*, 2007) The frequency of depressive features at 14.5% in the PD cohort is comparable to the 13.8% reported by Ravina et al,(Ravina, Camicioli, Como, *et al.*, 2007) in their study of depression in PD patients using the GDS-15. Depression in SWEDDs patients has not previously been investigated in depth, although research by Jang et al,(Jang, Ahn & Kim, 2013) seems to suggest that SWEDDs patients with depression are less severely affected than depressed PD patients. In contrast, our findings suggest a higher occurrence of depression in SWEDDs patients than in PD patients but that the severity of depression did not differ between these groups. Discrepancies between ours and Jang et al's results may be explained by our larger sample size and use of the GDS-15 rather than the Non-Motor

Symptoms Scale (NMSS), with the GDS-15 being a dedicated and validated questionnaire for detecting depressive features in Parkinson's Disease.(Ertan, Ertan, Kiziltan, *et al.*, 2005)

State and trait anxiety results for PD patients were consistent with one study of 46 PD patients(Mondolo, Jahanshahi, Granà, *et al.*, 2007) but inconsistent with another,(Yamanishi, Tachibana, Oguru, *et al.*, 2013) the differences may be accounted for by a combination of our lower mean disease duration, (0.69 vs 8.3 yrs) lower proportion of female patients (38.7% vs 60.7%) and patient drug naivety.

Autonomic symptoms were present across study groups, with gastrointestinal, urinary and thermoregulatory domains being the most common. A study into non-motor symptoms in de novo PD(Mollenhauer, Trautmann, Sixel-Döring, *et al.*, 2013) found scores for the SCOPA-AUT subdomains that are not dissimilar to ours. In the cardiovascular and gastrointestinal domains, SWEDDs were more severely affected than PD patients. Jang and colleagues(Jang, Kim, Cho, *et al.*, 2013) used MIBG myocardial scintigraphy to investigate cardiac sympathetic nerve denervation in SWEDDs and PD patients and found that SWEDDs were less affected than PD patients, but more so than controls. These findings would suggest that the cardiovascular complaints in the SWEDDs cohort are not related to cardiac sympathetic denervation, this, however, remains to be further investigated. Work by Cersosimo & Benarroch(Cersosimo & Benarroch, 2012) has suggested that autonomic dysfunction in neurodegenerative diseases may partly reflect Lewy-Body pathology in the autonomic nervous system. It remains to be ascertained if this is also the case in SWEDDs patients.

Silveira and colleagues'(Silveira-Moriyama, Schwingenschuh, O'Donnell, *et al.*, 2009b) investigation into olfaction in SWEDDs patients showed SWEDDs to have a normal sense of smell, significantly better than that of PD patients. Our study also found that SWEDDs had a better sense of smell than PD patients but differs in that olfaction in SWEDDs was worse

than in healthy controls. The strength of our study is in our larger SWEDDs population, although we did not account for smoking status or other factors that can affect olfaction.

The working diagnoses of the SWEDDs patients are consistent with suggested causes of the SWEDD phenotype.(Bajaj, 2010) This study is not sufficiently powered to assess non-motor symptoms in the individual diagnostic groups of SWEDDs patients, but it has shown the stability of non-motor symptoms in all patient groups over a two-year follow up period, a finding already documented in PD patients.(Erro, Picillo, Vitale, *et al.*, 2013)

Limitations of our study include that medication status was not taken into account for the follow up analysis but, given the lack of significant results, it is unlikely to have had a confounding influence. Moreover due to the ongoing nature of the PPMI study, data was not yet available for all patients at follow up, which somewhat restricted the size of the study population. In addition, the standard of truth for the working diagnoses of the SWEDDs patients was the clinical assessments of the study doctors. Finally, whilst a cut-off value of 5 for the RBDSQ may be most appropriate when investigating both PD patients and HC's,(Chahine, Daley, Horn, *et al.*, 2013b) because the questionnaire scores the presence of parkinsonism, it may overestimate the frequency of RBD in SWEDDs and PD patients.

In conclusion, our study has demonstrated a stable spectrum of non-motor symptoms in SWEDDs and PD over a two year follow up period. Our results suggest a difference between SWEDDs and early PD patients in key domains, particularly in daytime somnolence which is more severe and olfactory function which is only mildly affected. Further research should focus upon the pathological basis of SWEDDs parkinsonism and in vivo imaging of both dopaminergic and non-dopaminergic systems for a better understanding of the SWEDDs phenotype. This in turn will help classify SWEDDs patients correctly and differentiate them from PD and other forms of parkinsonisms.

Discussion: 950 words

Total word count~ 2812

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TABLE 1: *Baseline characteristics of study participants (Mean \pm SD)*

Variables		Diagnosis		
		Healthy controls	SWEDDs	Parkinson's Disease
Participants (n)		195	62	62
Age (yr)		63.0 \pm 11.1 _a	62.5 \pm 10.0 _a	63.3 \pm 9.1 _a
Gender (%)	Female	35.9%	38.7%	37.1%
	Male	64.1%	61.3%	62.9%
Disease duration (yr)			0.62 \pm 0.67 _a	0.69 \pm 0.70 _a
Hoehn and Yahr	1		36	28
Stage (n)	2		26	33
	3		0	1

Note: Values in the same row sharing the same subscript are not significantly different at $p < 0.05$ in the two-sided test of equality for column means. Tests assume equal variances.

TABLE 2 *Baseline questionnaire totals*

	Diagnosis			p values
	Healthy Controls	SWEDDs	Parkinson's Disease	
	(n=195)	(n=62)	(n=62)	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
ESS ^a	5.63 \pm 3.71	8.15 \pm 4.81	5.61 \pm 3.48	.001
GDS ^b	1.29 \pm 2.10	3.39 \pm 3.66	2.27 \pm 2.57	<.001
RBDSQ ^c	2.68 \pm 1.77	4.58 \pm 2.90	4.27 \pm 2.71	.001
STAI Y1 ^d	26.55 \pm 7.58	35.16 \pm 9.46	34.18 \pm 10.81	<.001
STAI Y2 ^e	27.40 \pm 5.33	34.89 \pm 9.91	33.42 \pm 9.99	<.001
SCOPA-AUT ^f	5.08 \pm 3.28	12.21 \pm 8.68	8.79 \pm 5.52	<.001
MDS-UPDRS 1 ^g	2.38 \pm 2.44	6.42 \pm 4.88	4.21 \pm 2.67	<.001
UPSIT ^h	35.03 \pm 4.44	31.26 \pm 6.30	21.82 \pm 8.12	<.001

a. Epworth Sleepiness Scale

b. Geriatric Depression Scale Short

c. REM Sleep Behaviour Disorder Screening Questionnaire

d. State-Trait Anxiety Inventory. Y1=State anxiety

e. State-Trait Anxiety Inventory. Y2= Trait anxiety

f. Scales for Outcomes in Parkinson's-AUTonomic (Excluding sexual domain)

g. MDS-UPDRS Patient Questionnaire One

h. University of Pennsylvania Smell Identification Test

TABLE 3: *Baseline prevalence (%) and severity of autonomic symptoms (Mean \pm SD)*

Domain	Healthy controls		SWEDDs		Parkinson's Disease		X ² p value
	Prevalence	Severity	Prevalence	Severity	Prevalence	Severity	
Gastrointestinal	40.0%	0.68 \pm 1.02	77.4%	3.06 \pm 3.09	82.3%	2.27 \pm 1.95	.001*
Urinary	91.8%	3.07 \pm 2.14	100%	4.98 \pm 3.35	93.5%	4.40 \pm 3.19	.067
Cardiovascular	15.9%	0.18 \pm .45	56.5%	1.08 \pm 1.42	38.7%	0.52 \pm 0.74	.001*
Thermoregulatory	52.3%	0.86 \pm 1.07	74.2%	2.45 \pm 2.41	66.1%	1.21 \pm 1.33	.004*
Pupillary	26.2%	0.3 \pm 0.5	43.5%	0.6 \pm 0.9	32.3%	0.4 \pm 0.7	.034*
Sexual ^a	41.3%	0.87 \pm 1.37	66.0%	1.79 \pm 1.75	50.0%	1.07 \pm 1.44	.007*

* Significant at p=0.05

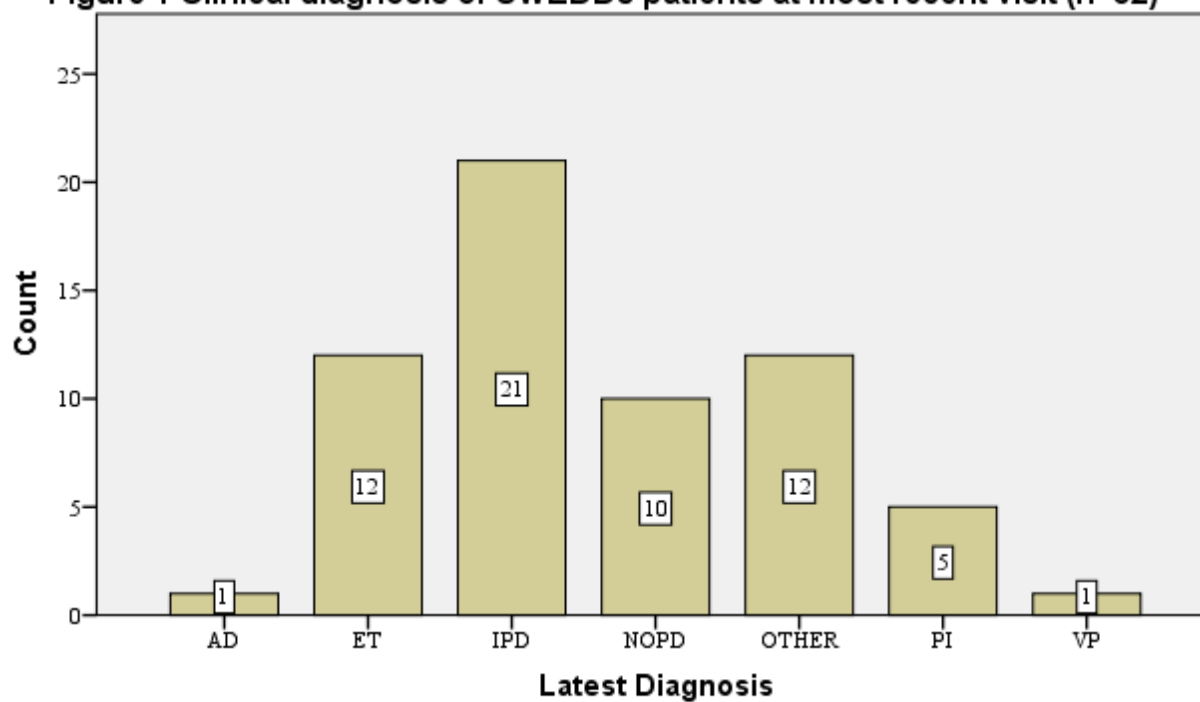
a For sexual analysis there were 167 HC's, 53 SWEDDs, 54 PD patients.

TABLE 4 *Clinical questionnaire totals of patients included in follow up analysis (Mean \pm SD)*

	Diagnosis											
	Healthy Controls (n=128)				SWEDDs (n=30)				Parkinson's Disease (n=36)			
	Visit				Visit				Visit			
	Baseline	Year 1	Year 2	P	Baseline	Year 1	Year 2	P	Baseline	Year 1	Year 2	P
ESS ^a	5.87±3.40	5.59 ±3.46	5.69±3.62	.809	7.87±5.03	6.70±4.76	6.77±5.05	.593	6.33±3.51	6.89±4.20	7.49±4.99	.760
GDS-15 ^b	1.34±2.38	1.21±2.14	1.10±1.91	.601	2.90±3.82	2.90±3.16	3.13±2.83	.493	2.06±1.82	2.23±1.78	2.11±2.13	.825
RBDSQ ^c	2.73±2.19	2.83±2.09	2.59±2.16	.552	4.07±2.64	4.23±2.70	4.03±2.91	.943	4.17±2.63	3.94±2.54	4.62±2.56	.471
STAI Y1 ^d	27.8±8.01	28.05±9.04	28.20±8.74	.906	35.07±10.36	33.57±11.18	31.97±9.19	.569	34.06±9.68	33.80±10.33	32.95±9.94	.882
STAI Y2 ^e	29.3±7.42	29.27±8.88	27.82±7.14	.194	35.00±11.37	33.83±10.30	34.27±10.14	.928	31.83±8.09	32.37±9.10	31.27±8.38	.801
SCOPA-AUT ^f	5.97±3.99	6.16±4.86	6.22±4.65	.964	11.67±9.45	12.43±8.94	12.30±8.53	.700	10.42±5.96	12.57±6.49	12.14±6.65	.238
MDS-UPDRS1 ^g	2.21±2.48	2.62±2.62	2.52±2.52	.315	5.00±4.42	5.33±4.06	6.17±4.73	.570	4.25±2.45	5.34±3.03	6.05±3.51	.471

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- a. Epworth Sleepiness Scale
 - b. Geriatric Depression Scale Short
 - c. REM Sleep Behaviour Disorder Screening Questionnaire
 - d. State-Trait Anxiety Inventory. Y1=State anxiety
 - e. State-Trait Anxiety Inventory. Y2= Trait anxiety
 - f. Scales for Outcomes in Parkinson's-AUTonomic
 - g. MDS-UPDRS Patient Questionnaire One

Figure 1 Clinical diagnosis of SWEDDs patients at most recent visit (n=62)



AD= Alzheimer's disease
ET= Essential tremor
IPD= Idiopathic Parkinson's Disease
NOPD= No PD nor other neurogenic disorder
PI= Psychogenic illness
VP= Vascular parkinsonism